

# Osteoarthritis and Cartilage



## The hereditary predisposition to hip osteoarthritis and its association with abnormal joint morphology

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### SUMMARY

**Objective:** Genetic factors and abnormalities of joint morphology are important in the aetiology of hip osteoarthritis (OA). The extent to which genetic influences are manifest through joint morphology has undergone limited investigation. Using a cohort with an hereditary predisposition to end-stage hip OA and a control group with no inherited risk, we aimed to identify associations with abnormal joint morphology and clinical features.

**Design:** One hundred and twenty-three individuals (mean age 52 years) with a family history of total hip arthroplasty (THA) (termed ‘sibkids’) were compared with 80 spouse controls. Morphology was assessed using standardised radiographs and cam, dysplasia, and pincer deformities defined. Regression modelling described the association of cohort with abnormal joint morphology, adjusting for confounders [age, gender, body mass index (BMI), OA, and osteophyte].

**Results:** Sibkids had an odds ratio of 2.1 [95%confidence interval (CI) 1.3–3.5] for cam deformity. There were no differences in the prevalence of dysplasia or pincer deformities. In both groups, hips with cam deformities or dysplasia were more likely to have clinical features than normal hips [odds ratio (OR) 4.46 (1.8–11.3), and 4.40 (1.4–14.3) respectively]. Pincer deformity was associated with positive signs in the sibkids but not in the controls (OR 3.0; 1.1–8.2).

**Discussion:** After adjustment for confounders that cause secondary morphological change, individuals with an hereditary predisposition to end-stage hip OA had a higher prevalence of morphological abnormalities associated with hip OA. Sibkids were more likely to demonstrate clinical features in the presence of pincer deformity, suggesting that the genes are acting not only through abnormal morphology but also through other factors that influence the prevalence of pain.

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### Introduction

Epidemiological studies indicate that hip osteoarthritis (OA) frequently occurs in the absence of OA in other joints, suggesting that local factors are important in its pathogenesis<sup>1–4</sup>. This implies that whilst ultimately similar pathological processes occur within all joints with advanced OA, local factors specific to the hip may be important in the initiation of the process. Drawing on earlier published theories<sup>5,6</sup>, Harris<sup>7</sup> suggested that subclinical

biomechanical factors were important in the development of hip OA. He rebuked theories that most cases of hip OA were “primary”, or “idiopathic”, and hypothesised that abnormal hip morphology predates onset of OA and is not secondary to the arthritic process<sup>7</sup>. Several studies<sup>8–14</sup> have since supported the hypothesis that some patients who are destined to develop end-stage OA have a pre-arthritic phase, which has recognisable features and may be amenable to intervention.

Specific abnormalities of hip morphology are recognised as biomechanical risk factors for the development of OA<sup>7–11,15</sup>. The predominant mechanisms are acetabular dysplasia, whereby the shallow acetabulum results in focal loading of articular cartilage beyond its physiological tolerance<sup>10</sup>, and femoroacetabular impingement (FAI)<sup>2,15</sup>, which occurs as a consequence of abnormal contact between the acetabular rim and femoral head–neck junction, injuring the chondrolabral junction. Together with improved

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understanding of these mechanisms, parameters have been introduced to quantify the deformities and classify patients with early hip disease<sup>5,16–19</sup>.

In spite of its clinical heterogeneity and multifactorial nature, the aetiology of hip OA has a significant genetic basis<sup>20</sup>. The increased risk to family members of patients with hip OA is well established<sup>21–26</sup>. Classic twin studies indicate a genetic contribution of 60% in women<sup>22,27</sup>. Linkage studies have identified regions of at least eight chromosomes as harbouring genes involved in the heritability of OA<sup>20</sup>.

In light of recent advances in understanding of mechanical factors in pre-arthritic hip disease, and genetic influences in OA, establishing whether the two are linked warrants consideration. Early studies by Wynne-Davis<sup>28</sup> confirmed the importance of genetics in acetabular dysplasia, and Rennie<sup>29</sup> noted that relatives of patients with slipped capital femoral epiphysis (SCFE) had a high prevalence of both the same condition and OA. Although it has been noted that some OA susceptibility genes are active in skeletal development<sup>30</sup>, there is no recent literature linking morphological abnormality, assessed using contemporary parameters, with genetic predisposition to hip OA. Investigating whether there is such an association is important as it may enable targeted investigation of the mechanisms by which genetic factors contribute to OA aetiology. Furthermore, morphological abnormalities may be readily screened for, and also can be surgically modified. For these reasons, if an association is proven then this offers great opportunities for identifying and tracking cohorts, and testing and validating biomarkers of early OA.

We hypothesized that the genetic predisposition to hip OA is associated with abnormalities of hip joint morphology. Using a cohort with an hereditary predisposition to hip OA and a control group with no inherited risk, we aimed to identify associations with abnormal joint morphology, and to establish whether morphological abnormalities were associated with the presence of clinical features and OA.

## Methods

### Cohorts

Subjects were enrolled from a prospective longitudinal study<sup>25,26</sup> of a cohort at risk of hip OA, and their spouse controls. These cohorts have been reviewed at baseline<sup>25</sup> and 5<sup>26</sup> years, and this report is based solely on data acquired from those participating at the 5-year review. The study had Institutional Review Board (IRB) approval and all subjects consented to participation. The reader is referred to our previous publication<sup>26</sup> for a detailed description of the construction of the cohorts. In summary, individuals from families in which two female siblings in the previous generation had undergone total hip arthroplasty (THA) for idiopathic end-stage OA were recruited. This group was termed the 'sibkid' cohort. Exclusion criteria for enrolment included significant trauma (hip injury requiring consultation with General Practitioner of Emergency department), or any history of predisposing factors to hip OA, such as developmental dysplasia, SCFE, and Perthes. No cases were excluded on these grounds.

### Clinical assessment

All subjects underwent clinical and radiographic assessment. Clinical assessment was performed by a single experienced orthopaedic fellow (TCBP). A proforma, completed by a research nurse, documented the findings in a standardised manner. Height and weight were recorded to calculate body mass index (BMI). All subjects were asked whether they had had surgery on either hip.

The presence of symptoms was defined by pain (suggestive of degenerative change) or clicking (suggestive of labral pathology) in either groin in the last 2 years necessitating investigation or treatment. A routine examination of the hips was performed and the presence of clinical signs defined by irritability on passive movement (groin pain on hip flexion, or on rotation at 90° of flexion) or a positive anterior impingement sign<sup>31</sup>, recorded as binary outcomes. Observer reliability of the clinical assessment was good<sup>26</sup>. Because the orthopaedic fellow that performed the clinical assessment also arranged the clinic appointments, it was not possible to blind him to the participant's sibkid or spouse status; however the clinical assessment was observed and documented independently by a research nurse, and was performed before radiographs were obtained.

### Radiographic assessment

#### Radiographic technique

All participants underwent a standardised supine anteroposterior (AP) pelvis radiograph to identify features of OA and evaluate acetabular morphology<sup>26</sup>. Feet positioning and centering of the beam was as recommended<sup>32</sup>. A 20 mm calibration ball was secured to the skin overlying the greater trochanter. In order to avoid rotated AP radiographs, the radiographer repeated the radiograph if necessary to ensure that the obturator foramen index was within 0.7–1.4<sup>33</sup>. In order to evaluate proximal femoral morphology, cross-table lateral radiographs of each hip were taken in 15° internal rotation<sup>32,34,35</sup>, using a 15° wedge placed beneath the femoral condyles to standardise rotation.

#### Grading of OA

All radiographs were scored by consensus<sup>36,37</sup> opinion of two experienced readers (a Consultant Musculoskeletal Radiologist, EGM, and an Orthopaedic Fellow, TCBP), as described elsewhere<sup>26</sup>. An overall OA grade was assigned using the Kellgren & Lawrence (K&L) system<sup>26,37</sup>. The repeatability for the minimum joint space width and osteophyte grading<sup>38</sup> was good<sup>26</sup>.

### Assessment of joint morphology

#### Continuous variables

Proximal femoral morphology was assessed from the lateral radiograph. The alpha angle<sup>18,19,32,39</sup> and anterior offset ratios (AOR)<sup>19,32,34</sup> were measured. Acetabular morphology was determined from the AP pelvis radiograph. The lateral centre-edge angle (CEA)<sup>5,32</sup>, acetabular index (AI)<sup>32</sup>, and acetabular depth:width ratio (ADWR)<sup>10</sup> were measured. These measurements were made using a custom software program, validated in previous studies<sup>8,19</sup>.

#### Categorical variables

To classify the morphology of each hip, reference ranges were applied to the continuous morphology measurements. A cam deformity was defined as an alpha angle > 62.5° or an AOR < 0.135<sup>19</sup>. Acetabular dysplasia is apparent when the femoral head is uncovered, the acetabulum shallow or the sourcil slopes excessively. Dysplasia was defined as a CEA < 19.7°, or an AI > 11.6°, or an ADWR < 0.40 (males) or < 0.42 (females). Global over-coverage (pincer deformity) was defined as a CEA > 39.9°, or an AI < -4.9°, or an ADWR of > 0.57 (males) or > 0.65 (females). These acetabular thresholds were derived from the same cohort as the proximal femoral parameters<sup>19</sup>, and are consistent with thresholds published elsewhere<sup>32,40</sup>. Focal over-coverage, which is a sub-type of pincer deformity caused by acetabular retroversion, was diagnosed by the presence of a cross-over sign<sup>32</sup>. Because of its

sensitivity to pelvic tilt<sup>32,41</sup>, we measured the sacrococcygeal joint to pubic symphysis (SCJ–PS) distance and only recorded the cross-over sign if the SCJ–PS distance was within 40–55 mm for females and 25–40 mm for males<sup>41</sup>. Assessment of global over-coverage was made in all subjects regardless of the SCJ–PS distance, as it was considered that referencing the margins of the sourcil<sup>32</sup> rather than the outermost point of the acetabular rim<sup>5</sup> would protect against error due to variation in pelvic tilt<sup>33</sup>. A pincer deformity was diagnosed if there was either focal or global over-coverage, or both.

All morphological measurements were made by one observer (TCBP). Radiographic scoring was performed blind to group status and clinical assessment after an interval of at least 4 weeks. Observer reliability was good<sup>31</sup>.

#### Outcomes and statistical analysis

There were two main analyses:

1. Association of cohort (sibkid vs control) with abnormal joint morphology.

The primary predictors were the sibkid and control cohorts. The outcome was abnormal joint morphology. Continuous values for each morphological parameter and categorical prevalence of each deformity were compared between the sibkids and controls.

2. Association of abnormal joint morphology with clinical features and radiographic hip OA.

The primary predictors were the morphological parameters (continuous and categorical). The outcomes were the presence of clinical features (determined by the clinical assessment of signs and symptoms, as described above), and the presence of OA (determined by whether the subject had K&L grade 2 or more OA). These analyses were performed for the sibkid and control groups separately and combined.

Population-averaged generalized estimating equations (GEE) logistic regression modelling was used to describe the association of each of the primary predictors with the outcomes. Analyses were adjusted for confounding variables. As each subject had two sets of morphological parameters (left and right hips), adjustment was made for clustering of hips, using linear regression for continuous outcomes and logistic for binary outcomes. Spouse age, sex and BMI were treated as potential confounders. Radiographic hip OA (K&L grade 2 or greater) was an additional confounder when fitting the model with morphological parameters<sup>42</sup>. In those hips with K&L grade 1 OA, superior femoral osteophyte was an additional confounder with regards to the proximal femoral parameters, and superior acetabular osteophyte with regards to the acetabular parameters, because accurate determination of the lateral margin of the sourcil may be harder in the presence of acetabular osteophyte<sup>43</sup>.

For all GEE models in which continuous variables were the outcome, assumption of normality was confirmed using histograms, the linearity assumption using fractional polynomials, and multicollinearity using variance inflation factors. All analyses were performed in Stata v11.1 (Stata, College Station, Tx, USA).

## Results

#### Cohort demographics

One hundred and twenty-three sibkids and 80 spouse controls were reviewed<sup>26</sup>. Demographics are shown in Table I.

**Table I**  
Demographics of the sibkid and control cohorts

Variable	Sibkids (n = 123)	Controls (n = 80)	P value
Mean age	52.3 (8.1)	54.1 (9.0)	0.15
Gender			
Male	62 (50%)	39 (49%)	
Female	61 (50%)	41 (51%)	0.82
Mean BMI	25.8 (4.2)	25.8 (4.6)	0.99

#### Hip morphology in sibkid and control groups

##### Proximal femur

Forty-three percent (106/246) of sibkid hips had a cam deformity, compared with 27% (43/160) control hips. A multivariable logistic GEE model adjusted for age, BMI, gender, and presence of K&L grade 2 OA or superior femoral osteophyte (K&L grade 1 hips), indicated that sibkids had an odds ratio (OR) of 2.1 [95% confidence interval (CI) 1.3–3.5] for cam deformity compared to controls (Table II).

##### Acetabulum

The acetabular morphology was normal in 80% (198/246) of sibkid hips and 75% (120/160) control hips. Seven percent (17/246) of sibkid hips were dysplastic compared to 8% (12/160) of control hips. Sibkids had an OR, adjusted for age, BMI, gender, presence of K&L grade 2 OA, and presence of superior acetabular osteophyte (K&L grade 1 hips) of 1.0 (0.37–2.73) for dysplasia (Table II). Thirteen percent of sibkid hips (31/246) had a pincer deformity compared to 18% (28/160) of control hips. Using the same model, sibkids had an OR of 0.57 (0.28–1.15) for pincer deformity (Table II). The higher prevalence of pincer deformity in the controls, in spite of similar continuous parameters (Table III), was not explained by a higher incidence of cross-over sign as only 5/160 (3%) control hips had a cross-over sign vs 16/246 sibkid hips (6.5%). None of these hips with cross-over signs were dysplastic based on the CEA, AI or ADWR<sup>44</sup>.

##### Combined joint morphology

Of the hips with cam deformities, 26/107 (24.3%) in the sibkid group also had an acetabular deformity (pincer or dysplasia), compared with 11/43 (25.6%) control hips ( $P = 1.000$ , Table IV). Although overall there was no difference in prevalence of acetabular deformity between the sibkids and controls, the sibkid hips with acetabular deformities also had cam deformities more frequently (26/48 hips, 54.1%) than the controls with acetabular deformities (11/40 hips, 27.5%,  $P = 0.017$ , Table IV).

#### Association of morphology and clinical features

##### Sibkids and controls combined

Eleven percent of hips (46/406) had positive clinical signs. Seven percent of hips (27/406) had positive signs and symptoms. Of the

**Table II**  
Population-averaged GEE logistical regression model describing the association of cohort (sibkid vs control) with morphological deformities

Outcome	Primary predictor	Multivariable sibkids OR (95% CI)
Cam deformity	Sibkid vs control	2.09 (1.25, 3.50)
Acetabular dysplasia	Sibkid vs control	1.00 (0.37, 2.73)
Pincer deformity	Sibkid vs control	0.57 (0.28, 1.15)

Multivariable logistic GEE model adjusted for age, BMI and gender, presence of radiographic OA. For acetabular morphology, presence of superior acetabular osteophyte (for K&L grade 1 hips) is an extra covariable, and for femoral morphology, presence of superior femoral osteophyte (for K&L grade 1 hips) is an extra covariable.

**Table III**

Mean values for the morphological parameters in the sibkid and control cohorts, estimated from the population-averaged GEE linear regression model

Outcome	Multivariable marginal mean (95% CI)	
	Controls	Sibkids
Lat CEA	30.42 (29.25, 31.59)	29.47 (28.52, 30.41)
AI	3.56 (2.64, 4.48)	4.34 (3.59, 5.08)
ADWR	0.52 (0.51, 0.53)	0.52 (0.51, 0.53)
Alpha angle	53.60 (51.47, 55.73)	58.50 (56.78, 60.22)
AOR	0.18 (0.17, 0.19)	0.17 (0.17, 0.18)

Multivariable random-effects linear regression adjusted for age, BMI and gender, presence of radiographic OA. For acetabular parameters, presence of superior acetabular osteophyte (for K&L grade 1 hips) is an extra covariable, and for femoral parameters, presence of superior femoral osteophyte (for K&L grade 1 hips) is an extra covariable.

205 hips (Table IV) with both normal femoral and acetabular morphology, only 4% (9 hips) had positive signs and 1% (three hips) had positive signs and symptoms.

Cam deformity was significantly associated with clinical features. These data are shown in Table V. With regards to acetabular morphology, both dysplasia and pincer deformities had ORs for the presence of clinical features greater than 1.75, but these were only statistically significant for dysplasia (Table V). This relationship was supported by the association of the individual acetabular morphological parameters with clinical features. For example, the OR for the association of AI with signs was 1.10 (1.02–1.18), indicating a 10% increase in risk of signs for every 1° increase in AI (Table V).

#### Sibkid and control subgroups

Fifteen percent of sibkid hips (38/246) and 5% of control hips (8/160) had positive clinical signs. Nine percent of sibkid hips (21/246) and 4% of control hips (6/160) had positive signs and symptoms. Of the 117 sibkid hips with both normal femoral and acetabular morphology, 7% (eight hips) had positive signs and 3% (three hips) had positive signs and symptoms. Of the 88 control hips with both normal femoral and acetabular morphology, 1% (one hip) had positive signs and none had positive signs and symptoms.

In both subgroups, cam deformity was significantly associated with clinical features (Table VI). The OR of clinical features, given acetabular dysplasia, was above 2.7 in both subgroups but the smaller numbers prevented statistical significance (Table VI). For pincer deformity, association with clinical features was only apparent in the sibkids and not in the controls (Table VI). In fact, none of the 28 control hips with pincer deformities had clinical features. The interaction of femoral and acetabular morphology is likely to be important in determining whether individual abnormalities result in clinical features. Potentially the higher prevalence of clinical features in the sibkid hips with pincer deformities could be due to a co-existing cam deformity, which occurred more

**Table IV**

Association analysis of the combinations of acetabular and femoral morphology in the sibkids and controls. Logistic regression model

Morphology		Group		Sibkids OR (95% CI)
Femur	Acetabulum	Sibkid hips (%)	Control hips (%)	
Normal	Normal	117 (47.6)	88 (55.0)	1.00 (1.00–1.00)
Normal	Dysplasia	7 (2.8)	7 (4.4)	0.75 (0.25–2.20)
Normal	Pincer	15 (6.1)	22 (13.8)	0.51 (0.25–1.04)
Cam	Normal	81 (32.9)	32 (20.0)	1.86 (1.14–3.06)
Cam	Dysplasia	10 (4.1)	5 (3.1)	1.49 (0.49–4.52)
Cam	Pincer	16 (6.5)	6 (3.8)	1.99 (0.75–5.29)

**Table V**

Association between joint morphology and presence of positive clinical signs on examination, and signs and symptoms, for both sibkids and controls. GEE population-averaged logistic regression analysis

Primary predictor	Multivariable OR for presence of signs (95% CI)	Multivariable OR for presence of signs & symptoms (95% CI)
Cam deformity	3.17 (1.57, 6.39)	4.46 (1.76, 11.31)
Acetabular dysplasia	3.23 (1.14, 9.16)	4.40 (1.36, 14.28)
Pincer deformity	2.21 (0.85, 5.76)	1.76 (0.54, 5.76)
Lat CEA	0.94 (0.89, 1.00)	0.92 (0.86, 0.99)
AI	1.10 (1.02, 1.18)	1.10 (1.01, 1.21)
ADWR*	0.70 (0.50, 0.96)	0.59 (0.39, 0.89)
Alpha angle	1.05 (1.02, 1.08)	1.08 (1.04, 1.12)
AOR*	0.81 (0.47, 1.40)	1.15 (0.58, 2.29)

Multivariable logistic GEE model adjusted for age, BMI, gender, sibkid or control status and presence of radiographic OA. For acetabular parameters, presence of superior acetabular osteophyte (for K&L grade 1 hips) is an extra covariable, and for femoral parameters, presence of superior femoral osteophyte (for K&L grade 1 hips) is an extra covariable.

\* Change in 0.05 units.

commonly in the sibkids than controls (Table IV). However, only three of the eight sibkid hips with positive signs and a pincer deformity also had a cam deformity. Furthermore, of the 37 hips with pincer deformities and normal femoral morphology, none of the 22 from the control group had clinical features, whilst five of the 15 from the sibkid group had positive signs ( $P = 0.007$ ). The highest rate of clinical features occurred in hips with cam combined with dysplasia deformities (5/15 hips had positive signs).

Potentially, variation in prevalence of clinical features given a deformity could be explained by the deformities being more severe in either subgroup. However, the mean alpha angle in the cam hips was 70.5° (69.1°–72.0°) in the sibkids and 68.9° (66.1°–71.7°) in the controls, in the dysplastic hips the mean lateral CEAs were 16.3° (14.8°–17.8°) and 16.2° (13.7°–18.6°) respectively, and in the pincer hips the mean lateral CEAs were 42.6° (41.6°–43.6°) and 42.6° (40.9°–44.3°) respectively.

#### Association of morphology and presence of OA

Overall, 12% (48/406 hips) had K&L grade 2 OA. A multivariable logistic GEE model adjusted for age, BMI, gender, sibkid or control status, with additional adjustment for superior femoral osteophyte (cam deformity) or superior acetabular osteophyte (acetabular deformity), gave ORs of 1.13 (0.58–2.22) for a cam deformity and OA, 0.44 (0.06–3.34,  $P = 0.429$ ) for dysplasia and OA, and 2.38 (1.08–5.25) for pincer deformity and OA.

**Table VI**

Association between joint morphology and presence of positive clinical signs on examination, and signs and symptoms, subdivided by sibkid and control groups. GEE population-averaged logistic regression analysis

Primary predictor	Group	Multivariable OR for presence of signs (95% CI)	Multivariable OR for presence of signs & symptoms (95% CI)
Cam deformity	Controls	6.37 (1.13, 36.09)	13.02 (1.30, 130.52)
	Sibkids	2.75 (1.27, 5.97)	3.38 (1.18, 9.64)
Acetabular dysplasia	Controls	4.22 (0.51, 34.73)	6.54 (0.69, 62.09)
	Sibkids	2.72 (0.77, 9.60)	3.39 (0.72, 16.00)
Pincer deformity	Controls	—	—
	Sibkids	3.02 (1.11, 8.21)	2.53 (0.72, 8.83)

Multivariable logistic GEE model adjusted for age, BMI, gender, sibkid or control status and presence of radiographic OA. For acetabular morphology, presence of superior acetabular osteophyte (for K&L grade 1 hips) is an extra covariable, and for femoral morphology, presence of superior femoral osteophyte (for K&L grade 1 hips) is an extra covariable.



Fifteen percent (36/246) of sibkid hips and 8% (12/160) of control hips had K&L grade 2 OA. Having subdivided the group according to sibkid or control status, application of the same GEE model provided similar ORs for the association of OA and each deformity, but statistical significance was lost due to the smaller numbers.

## Discussion

This study demonstrated that a cohort with an hereditary predisposition to end-stage hip OA had a higher prevalence of abnormalities in hip morphology associated with the development of hip OA, compared with a control group. In both groups, cam and dysplasia deformities were associated with clinical features, suggesting these abnormalities are clinically relevant. In the presence of pincer deformity, the sibkids demonstrated clinical features but the controls did not, suggesting that genetic factors act not only through abnormal morphology but also other factors that may influence prevalence of pain.

The difference in prevalence of cam deformity was striking, with an OR greater than two. Cam deformities are associated with cartilage damage to the anterosuperior acetabulum<sup>2</sup>. Overall, there was no difference in prevalence of abnormal acetabular morphology. However, in the sibkids, over half of those hips with acetabular deformity also had a cam deformity, whereas in the controls, acetabular deformity usually occurred in isolation. Clearly, the end-result of morphological abnormalities of the hip depends on the interaction of the acetabulum and proximal femur. The majority of FAI patients have mixed FAI, combining both cam and pincer deformities<sup>2</sup>. However, Cobb *et al.*<sup>45</sup> suggest that cam deformity is usually associated with a shallow acetabulum. Evolutionary studies support this, with mammals with high hip loading benefiting from the strength of a thick femoral neck with an aspherical head articulating in a shallow acetabulum<sup>46</sup>. Consequently, one may have expected to see a higher prevalence of dysplasia in the sibkids than controls. The continuous acetabular parameters were marginally more towards dysplasia in the sibkids, and the categorical data showed a slightly higher prevalence of pincer deformity in the controls. Potentially cam deformities in combination with either dysplasia or pincer deformity may result in damage to the joint, but through subtly different mechanisms.

Cam deformities were strongly associated with clinical features in both groups. Interestingly, the controls had higher ORs. This observation was not due to more severe cam deformity in the controls, nor because the control cam hips were associated with an acetabular deformity more frequently, as approximately one-quarter of sibkid and control cam hips had a co-existing acetabular deformity. The significantly higher prevalence of cam deformity in the sibkids may explain why the ORs for clinical features were lower, as increasing size of the denominator will reduce the OR. Also this observation was cross-sectional and some of the sibkid cam hips may develop signs in the future. Probably the most important influence on the ORs was that virtually none of the morphologically normal control hips had clinical features whereas some of the sibkid hips did.

On the acetabular side, parameters associated with dysplasia were associated with clinical features, whereas none of the controls with pincer deformity manifested clinical features. This suggests that in these cohorts, dysplasia may be more clinically important than pincer deformity although the subgroups are too small to draw definitive conclusions. The higher prevalence of clinical features given a pincer deformity in the sibkids compared to controls could be due to variation in the femoral anatomy. However, only three of eight pincer hips with signs also had a cam deformity, and clinical features remained more common in the sibkids when

the femoral morphology was normal. The higher prevalence of clinical features in the sibkids suggests that the inherited risk is manifest not only through morphology but other factors which may modulate disease progression. These factors may include the vulnerability of the articular cartilage and labrum to injury and more detailed imaging with magnetic resonance imaging (MRI) could answer this question. These results are similar to those of a sibling study of FAI<sup>31</sup>, and indeed Waarsing *et al.*<sup>30</sup> have suggested that OA risk alleles increase the vulnerability of cartilage for non-optimal bone shapes. Alternatively, genetic differences in pain processing may explain the higher prevalence of symptoms.

With regards to association with radiographic OA, we observed a weak association of cam deformity and OA. However, the fact that signs and symptoms were present in the absence of radiographic OA may indicate pre-arthritis change, and longer term follow-up may reveal stronger associations of this deformity and radiographic OA. On the acetabular side, it was pincer deformity, not dysplasia, which was associated with OA. The radiographic assessment of acetabular coverage may be prone to error and hips with impingement may develop secondary ossification of the acetabular labrum<sup>31,43</sup>. We attempted to minimise such error by adjustment for acetabular osteophyte. However, it is conceivable that subtle alterations in radiographic appearances secondary to OA (for example sclerosis at the lateral rim of the acetabulum or ossification of the labrum), which are not classically osteophytic in appearance may bias the assessment of acetabular coverage and could potentially explain this result. In fact, Corten *et al.*<sup>43</sup> have suggested that bone formation at the acetabular rim can occur as a continuum of a degenerative process, distinct from osteophyte formation. Nevertheless, this result is interesting in the context of pincer deformities being associated with clinical features in the sibkids but not controls, which may signify disease progression to early OA.

This study had a number of strengths and weaknesses. All subjects had clinical and radiological screening of their hips, ensuring detection of subclinical deformity and positive examination findings in asymptomatic individuals. Reliability of the clinical assessment was demonstrated previously<sup>26</sup>. Our statistical analysis adjusted for potential confounders. Cam deformities are commonly bilateral<sup>39</sup>, therefore it was important to adjust for clustering of hips. The prevalence of cam and pincer morphologies vary between sexes<sup>15</sup>, and it is not known what affect age or BMI has on joint morphology. Therefore age, gender, and BMI were adjusted for. Longitudinal data regarding occupation and leisure activities were not available, and we acknowledge that sporting activity during adolescence may modify morphology<sup>47</sup> and have a familial pattern. In early OA, secondary osteophyte formation at the femoral head–neck junction may be misinterpreted as a cam deformity. In late OA, femoral head collapse and osteophyte may cause secondary morphological change of the joint<sup>42</sup>. Such confounding was reduced by the relatively young age of the study groups, the fact that few cases had advanced OA, and the statistical adjustment for osteophytes and OA. As mentioned above, this adjustment may not have been completely adequate and ideally, our baseline assessment of morphology would have occurred at the onset of skeletal maturity. Pollard *et al.*<sup>31</sup>, in a sibling study of femoroacetabular impingement, noted that many siblings of patients treated for cam impingement also had cam deformities themselves, in the absence of degenerative change. Whilst both that and the current study were cross-sectional in design, we suggest that cam deformities may indeed be inherited and may predate alterations in morphology due to OA. Further follow-up is needed to see whether the morphological associations observed at this time-point result in OA in the future.

The sibkid cohort was constructed from families with two female sibling pairs with end-stage hip OA, which was considered

to have been 'idiopathic' in its aetiology. Cases with secondary OA were excluded. Assessment of morphology in the siblings was not possible due to the lack of available radiographs and the advanced nature of their OA which prevented valid morphological assessment. Spencer *et al.*<sup>25</sup> originally chose female sibling pairs because of the observation of shared genetic heritability between female patients with Heberden's nodes and hip OA<sup>48,49</sup>. As there was no morphological pre-selection of the cohort, it is interesting that the prevalence of cam deformity was so high, given its predilection to males rather females<sup>15</sup>.

The control group for a familial risk study should ideally have a similar demographic profile and exposure to environmental factors whilst differing from the familial group with respect to possible genetic determinants. Furthermore, controls should be representative of the general population in terms of their susceptibility to disease. Frequently, studies employ spouses or partners as controls as they fulfil these criteria. By their common and long-standing proximity to the index case, spouses share a common environment, and similar positive or negative biases and selection criteria for intervention. In this study, pre-selection for morphological sub-types potentially influenced by environmental factors, such as sporting activity, and ascertainment bias with respect to symptoms, could have affected the controls, however this is likely to affect the siblings in a similar manner, thereby not changing the ORs significantly.

The limitations of radiography compared to three-dimensional imaging, the necessity for radiographic standardisation, measurement error, and parameter thresholds have been discussed previously<sup>19,26,31,50</sup>. Overall, only 55% and 48% of control and sibling hips respectively were classified as morphologically normal on both the femoral and acetabular sides, using parameter thresholds applied previously and successfully<sup>31</sup>. The use of more than one parameter to define a particular pathoanatomy may increase sensitivity at the expense of specificity. Whilst this prevalence of 'abnormality' does seem high, the control prevalence of cam, pincer and dysplasia deformities was similar to other studies<sup>31,51,52</sup> and it has been suggested that subtle morphological abnormalities are common because OA generally occurs after reproductive age thus limiting its influence in evolutionary selection<sup>46</sup>. Alteration of parameter thresholds is unlikely to change the ORs significantly<sup>31</sup>. In fact, applying alpha angle thresholds of 50°, 55° and 67° for a cam deformity, resulted in unadjusted ORs of 1.85, 1.71, and 3.1 respectively (all statistically significant).

In conclusion, the hereditary predisposition to hip OA was associated with morphological abnormality of the hip joint. Cam deformity was the most important association, although the interaction with acetabular deformity warrants further study. Investigation of the importance of mechanical factors as a causative influence in the genetic aetiology of hip OA appears justified. The genetic influence was also associated with clinical features beyond morphological abnormality. Therefore the role of genetics in both the vulnerability of cartilage to injury, and pain processing, is worthy of further study.

#### Author contributions

All authors made substantial contributions to:

- (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data,
- (2) drafting the article or revising it critically for important intellectual content,
- (3) final approval of the version to be submitted.

Specifically:

T. Pollard: analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual

content, final approval of the article, provision of study materials or patients, administrative, technical, or logistic support, collection and assembly of data.

R. Batra: statistical expertise, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article.

A. Judge: statistical expertise, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article.

B. Watkins: provision of study materials or patients, administrative, technical, or logistic support, collection and assembly of data, drafting of the article, final approval of the article.

E. McNally: collection and assembly of data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article.

H. Gill: drafting of the article, critical revision of the article for important intellectual content, final approval of the article, administrative, technical, or logistic support, collection and assembly of data.

G. Thomas: drafting of the article, critical revision of the article for important intellectual content, final approval of the article, administrative, technical, or logistic support.

S. Glyn-Jones: analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article.

N. Arden: analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article.

A. Carr: obtaining of funding, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, provision of study materials or patients, administrative, technical, or logistic support.

In addition to Mr. T. Pollard, Professor A. Carr takes responsibility for the work as a whole from inception to finished article.

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#### Conflict of interest statement

None of the authors have any commercial conflict of interest to declare which is of relevance to this manuscript. Professor Carr, Professor Arden, and Dr. Gill, and Mr. Glyn-Jones may use the findings of this study to support further research grant applications.

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